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Child Abuse and Neglect as Risk Factor for Comorbidity Between Depression and Chronic Pain in Adulthood

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Abstract:	It is estimated that comorbidity between depression and chronic pain reaches more than half of the cases of depressed adult patients around the world. Evidence indicates that some stressors, such as Early-Life Stress (ELS), mediate the co-occurrence of depression and chronic pain. This study aimed to assess whether ELS or any of its subtypes could be considered as risk factors for comorbidity between depression and chronic pain. For this purpose, n=44 patients in depressive episode were evaluated, which n=22 were diagnosed with depression and chronic pain, and the other n=22 patients were with depression, but depressive without chronic pain. Results had shown that ELS occurrence is more significant among depressive patients with chronic pain compared to those without pain. When subtypes of ELS was evaluated, the group of depressive patients with pain showed significantly higher prevalence of emotional neglect than those depressive participants without pain. Data analysis have shown that severity of the depressive symptoms has a significant impact on the total score of childhood trauma, emotional abuse, physical abuse, emotional neglect, and physical neglect. Also, that emotional abuse, sexual abuse, and physical neglect have significant impact on the severity of depression. In conclusion, our findings indicate that ELS can be considered as a risk factor for the comorbidity between depression and chronic pain.

CHILD ABUSE AND NEGLECT AS RISK FACTOR FOR COMORBIDITY BETWEEN DEPRESSION AND CHRONIC PAIN IN ADULTHOOD

ABSTRACT

It is estimated that comorbidity between depression and chronic pain reaches more than half of the cases of depressed adult patients around the world. Evidence indicates that some stressors, such as Early-Life Stress (ELS), mediate the co-occurrence of depression and chronic pain. This study aimed to assess whether ELS or any of its subtypes could be considered as risk factors for comorbidity between depression and chronic pain. For this purpose, n=44 patients in depressive episode were evaluated, which n=22 were diagnosed with depression and chronic pain, and the other n=22 patients were with depression, but depressive without chronic pain. Results had shown that ELS occurrence is more significant among depressive patients with chronic pain compared to those without pain. When subtypes of ELS was evaluated, the group of depressive patients with pain showed significantly higher prevalence of emotional neglect than those depressive participants without pain. Data analysis have shown that severity of the depressive symptoms has a significant impact on the total score of childhood trauma, emotional abuse, physical abuse, emotional neglect, and physical neglect. Also, that emotional abuse, sexual abuse, and physical neglect have significant impact on the severity of depression. In conclusion, our findings indicate that ELS can be considered as a risk factor for the comorbidity between depression and chronic pain.

Key-words: *Depression; Chronic Pain; Early-Life Stress (ELS); Emotional Neglect; Abuse; Neglect*

BACKGROUND

Currently, depression is considered the most disability disease (WHO, 2017). It is a chronic and highly recurrent disorder, which affects the quality of life of millions of people around the world (Andrade et al., 2012; Fleck et al., 2009; Kessler et al., 2003; Viana & Andrade, 2012). Although studies have shown the efficacy of psychotherapy and medication for handling depression (Gartlehner et al., 2016; Tursi et al. 2013), about 30%-50% of patients do not respond to current treatments (Mari et al. 2013; Wooderson et al., 2011). Moreover, depression has been associated with some biological impairment, such as altered vascular and autonomic functions, hypercoagulability and hyperactivity of hypothalamus-pituitary-axis (HPA) (Juruena et al., 2004; Juruena et al., 2018; Menezes et al, 2019). This association is the reason why depression may be considered and treated as a systemic disorder (Juruena, 2014). Evidence shows that depression in adulthood is related to a higher risk for comorbid diseases, and these comorbidities are associated to worse prognosis and limited response to treatment (Geiss et al., 2010; Mari et al., 2013). One of the comorbidities that must be considered in depression is the chronic pain (DeVeaugh-Geiss et al., 2010; Fishbain et al., 1997; Gambassi, 2009; Knaster et al., 2016; Watson et al., 2009). According to the literature, chronic pain occurs in more than half of the cases of depression (Askari et al., 2017; Bair et al., 2008; Gambassi, 2009), it is related to lower responsiveness to treatment, and a worse prognosis for both disorders (DeVeagh-Geiss et al., 2010). It is difficult to establish whether pain or depression appears first, but studies suggested the influence of psychosocial factors as one of the hypothesis for explaining this interaction (Goesling et al., 2013; Gambassi, 2009; Gatchel, 2004; Campbell et al., 2003). So, many factors such as: neural activation pathways (Linton & Bergbom, 2011; Jann & Slade, 2007), catastrophic and hopelessness cognitions (Lintonl et al., 2011; Mystakidou et al., 2007), and impairment of interpersonal relationships (Teasell & Bombardier, 2001) may, jointly, predispose the emergence of comorbidity between depression and chronic pain. Further variables already described, stress has also been considered a psychosocial factor that plays an essential role in the development of many diseases, acting as a precipitator (Mello et al., 2007). Blackburn-Munro & Blackburn-Munro (2001) considered chronic stress as a link between pain and depression, and that significantly threatens normal operation of the human body physiology, which is stable by certain biological mechanisms; and a stable environment that the human belongs to (Blackburn-Munro, 2004). Besides chronic stress, which lasts throughout life, Early-

life Stress (ELS), also plays a relevant role in emergence of several disorders (Juruena, 2014; Juruena et al., 2015; Tofoli et al., 2011), including depression and pain (Carr et al., 2013; Davis, Luecken & Zautra, 2005; Lampe et al., 2003; Van Houdenhove, Luyten & Egle, 2009). ELS is defined as an exposure to traumatic events in early-life (childhood and adolescence), which consequences may last even in adulthood, resulting in psychiatric disorders and impairment of quality of life (Carr et al., 2013; Juruena et al., 2014; Martins et al., 2014). It is known that ELS interferes in aspects of emotional, cognitive, social, and neuroendocrine constitutive elements of a person, in addition of propitiating anatomical-functional changes in brain structures, impairing development at all stages of life (Heim et al., 2004; Norman et al., 2012; Teicher et al., 2003; Teicher, 2002; Teicher et al., 2012). Some examples of ELS are parent death or divorce, substance abuse, psychiatric disorders in caregivers, abuses (emotional, physical and sexual), and neglects (emotional and physical) (Carr et al., 2013; Juruena, 2007; Bernstein et al., 1994, 2003). Then, the goal of the present study was to assess if ELS or its subtypes (and which of them) are more likely to be experienced by depressed patients with chronic pain, compared to those without chronic pain.

MATERIAL AND METHODS

Study Design

This study had a transversal, case-control, observational design. The project was approved by Research Ethics Committee of Faculty of Philosophy, Sciences, and Letters of Ribeirao Preto in a partnership granted with Research Ethics Committee of Clinics Hospital of Ribeirao Preto (Protocol nº 55266716.2.0000.540) and followed the ethical principles of the Declaration of Helsinki and the standards of Brazilian National Health Council (CNS 466/12).

Sample

The sample was composed of n=44 patients in a current depressive episode, which n=22 presented chronic pain, and n=22 did not. The sample recruitment was non-randomized, and patients came from psychiatric ambulatory of Clinics Hospital of Ribeirao Preto, São Paulo, Brazil. All participants were admitted based on the following criteria: age between 18 - 65 years-old; having read, comprehended, and signed the Consent Form; being in a current depressive episode diagnosed by more than one psychiatrist, and presenting,

assessed by GRID-HAM-D_{21}, depressive symptoms severity classified at least as moderate level. The criteria for inclusion in the depressive group with chronic pain was, besides moderate or more severe depression, having chronic pain diagnosed by clinicians for at least six months. The patients that presented intellectual disability, cognitive deficit, progressive degenerative disorders, or neurological disorders fulfilled the exclusion criteria of the study. Also, patients were excluded from this study if they presented acute psychotic episode, depressive episode preceded only by psychotic episodes or other general medical conditions.

Instruments and Procedures

All forty-four participants that fulfilled the inclusion criteria were assessed by the protocol of instruments – sociodemographic elaborated by researchers, clinical, and psychiatric standard questionnaires. Also, all sample answered to validated questionnaires that assessed the presence or absence of ELS and chronic pain.

Assessment of Depression

For confirming the diagnosis of the current depressive episode and the existence of other possible psychiatric comorbidities, subjects were assessed by MINI INTERNATIONAL NEUROPSYCHIATRIC INTERVIEW - Brazilian Version 5.0.0. (Mini-Plus; Amorim, 2000; Sheehan et al., 1998). We applied GRID Hamilton Depression Rating Scale (GRID-HAM-D_{21}) to evaluate the levels of depression in all subjects (Williams et al., 2008; Henrique-Araújo et al., 2014).

Assessment of Chronic Pain Brief Pain Inventory (BPI)

Brief Pain Inventory (BPI) was developed by Daut, Cleeland & Flanery (1983) and adapted for the Brazilian population by Menezes et al. (2017). This instrument was applied for assessing chronic pain in the sample and is a questionnaire with multidimensional characteristics, which evaluates, briefly and integrally, the pain felt by the subject in the last 24 hours. It takes into account the pain treatment, relief, location in the body, and interference in subjects' quality of life (Cleeland, 1985). BPI first question is dichotomous, a 'yes' or 'no' question, for assessment of the presence or absence of chronic pain, important for location subjects in study groups. Depressive patients that answered 'yes' to the first question were located in the chronic pain group and continued answering BPI following questions.

Assessment of ELS

For assessing ELS, Childhood Trauma Questionnaire (CTQ) (Bernstein et al., 2003) was applied. This instrument can be applied in subjects that are over 12 years-old (Bernstein et al., 2003). In this study, it was applied the adapted and validated version for Brazilian population, which consists in 28 sentences with the same psychometric proprieties as the first validated instrument (Grassi-Oliveira et al., 2014). The version applied in this study was self-applicable, and assesses five subtypes of ELS, as described by Bernstein et al. (2003): emotional abuse (EA), physical abuse (PA), sexual abuse (SA), emotional neglect (EN), and physical neglect (PN) (Grassi-Oliveira et al., 2014). EA is defined as any form of devaluation or offence that humiliates and/or threatens child's well-being. PA is characterized as a physical attack with the possibility of resulting in injuries and physical damage. SA is described as a sexual manifestation, both by conduct and/or contact. EN is the failure of the caregiver in providing psychological well-being. PN is characterized by the inability of the caregiver providing primary care of the child, such as food, shelter, and safety (Bernstein et al., 1994, 2003). Each sentence in the instrument presents a Likert scale structure, which scores vary from 1 (never) to 5 (always). Each subtype of ELS is classified as may give a final score from 5 to 25, and presents a particular cut-off point for each one. The severity of each subtype of ELS is classified as "not existent", "weak to moderate", "moderate to severe", "severe to extreme", varying from 5-25 points, according to instrument Brazilian validation (Grassi-Oliveira et al., 2014). According to Bernstein et al. (2003), subtypes of ELS that presented scores 'moderate to severe' or higher, must be considered as a subtype of ELS experienced by the subject. Nevertheless, scores classified as 'weak to moderate' or lower must not be considered as a subtype of ELS. The subject must have experienced at least one subtype of ELS to be considered as a subject with history of ELS (Bernstein et al., 1994, 1997, 2003; Carpenter et al., 2007).

Statistical Analysis

For data analysis, SPSS software 23.0 (Statistical Package for the Social Science, version 23.0) was applied. For continuous data, when parametric, Student t test or One-way ANOVA (one factor) or Two-Way ANOVA was applied. When the continuous data were non-parametric, Mann-Whitney or Kruskal-Wallis (one factor) or Friedman test (two factors); for categorical data, chi-square (χ^2) was applied. The descriptive data, when continuous, were presented by mean and standard deviation (SD); when categorical, data was presented by number of participants and percentage (%). *Posthoc* test applied was

Tukey test. Lastly, for observing the possible association between two variables, Odds Ratio (OR) was applied. The OR was also used to analyse whether the presence of ELS or any of its subtypes, may be considered a risk factor for comorbidity between pain and depression. The significance level considered was $p \leq 0.05$ and confidence interval (C.I.) was 95%.

RESULTS

Sociodemographic and clinical characteristics of sample

The groups, depressed patients with (n=22) and without (n=22) pain, were matched by gender and age. No significant differences were found for those and the others sociodemographic variables assessed, as shown in Table 1.

Insert Table 1

About clinical and psychiatric features, there was no significant difference in polarity of depression (unipolar and bipolar), Both groups, with and without pain, were mainly, composed by unipolar depressive patients ($p=0.34$). Depression onset age also presented a tendency of difference between groups ($p=0.07$) – the mean age of first depressive episode of chronic pain group was 24.82(±7.38) years-old, and the group without pain was 23.27(±12.74) years-old. These two groups also did not show differences in the number of suicide attempts ($p=0.87$), psychiatric hospitalization ($p=0.17$), and prevalence of psychiatric disorders among relatives ($p=0.68$). Although, patients with chronic pain presented a higher number of clinical disorders ($p \leq 0.001$) and psychiatric comorbidities ($p=0.02$) than patients without pain, as shown in Table 2. Depressive patients with chronic pain presented the following psychiatric comorbidities: Anxiety disorders (n=7; 31.8%); Posttraumatic Stress Disorder (PTSD) (n=3; 13.6%); Cluster B Personality Disorders (n=11; 50%); Eating Disorders (n=1; 4.5%); Conversion Disorders (n=1; 4.5%); Hypochondria (n=2; 9.1%); and Somatoform Pain Disorder (n=15; 68.2%). Depressive patients without pain presented the following comorbidities: Anxiety disorders (n=10; 45.5%); Obsessive Compulsive Disorder (OCD) (n=1; 4.5%); Cluster B Personality Disorders (n=7; 31.8%); Conversion Disorders (n=1; 4.5%); and Hypochondria (n=1; 4.5%). When comparing the comorbidities between groups, there was a higher prevalence of somatoform pain disorder in depressive patients with chronic

pain (χ^2=22.75; *d.f.*=1.0; p≤0.001). There was a tendency of PTSD of being more prevalent in chronic pain group (χ^2=3.22; d.f=1.0; *p*=0.07).

Insert Table 2

Considering severity of depression symptoms, when comparing the group with and without pain by results of GRID-HAM-D_{21}, the mean of the group with pain (24.05 ±4.70) was significantly higher than without pain (20.23 ±3.89) (t=2.93; *d.f.*= 42.0; *p*=0.005).

Regarding pain symptoms, depressive patients with chronic pain had a severity and interference of pain assessed by BPI. Concerning the intensity of the pain, results showed that, in the last 24 hours, the mean total score of participants with pain in this study was 23.91 (±9.66) which represents 59.77% of the total. In relation to pain interference in the last 24 hours patients with pain reached a mean score of 57.50 (±9.45), that represents 82.14% of the total score of BPI for this dimension.

ELS and its subtypes in sample

As shown in Fig. 1a, subjects with chronic pain experienced more ELS events than the group without pain (81.8% vs. 54.5%; χ^2= 3.77; *d.f.* =1.0; *p*=0.05). Applying OR, subjects with chronic pain were 3.75 times more likely of having experienced ELS (OR: 3.75; CI 95%; 0.95-14.76).

Insert Fig 1a

The patients were also assessed for depression, presence or absence of ELS and pain. The results shows that patients with depression, ELS and pain present more severe symptoms of depression compared to other subgroups. Fig1b. shows results of GRID-HAM-D21 for all 4 subgroups of the study (ELS/PAIN, ELS/NO PAIN, NO ELS/PAIN, NO ELS/NO PAIN) (F=2.753; d.f: 3.0; p=0.055; posthoc test [NO PAIN/NO ELS x PAIN/ELS]: -4.650; p=0.046) and a table of the same figure thar is showing GRID-HAM-D21 mean and SD for each of the subgroups (NO PAIN/NO ELS 19.00 ± 2.49; NO PAIN/ELS 21.64 ± 4.63; PAIN/NO ELS 24.33 ± 4.51; PAIN/ELS 23.65 ± 4.98).

Insert Fig 1b

Assessing OR, subjects with chronic pain presented 3.75 times higher risk of having experienced EN than those without pain (OR: 3.75; CI 95%; 1.07-13.07). On the other hand, other subtypes of ELS, when comparing groups with and without pain, did not show any significant difference: EA (54.5% vs. 50%; χ^2= 0.09; *d.f.*=2.0; *p*=0.76), PA (40.9% vs. 36.3%; χ^2=0.58; *d.f.*=2.0; *p*=0.45), SA (36.6% vs. 22.7%; χ^2=1.62; *d.f.*=1.0; *p*=0.44), and PN (45.5% vs. 40.9%; χ^2=0.0; *d.f.*=1.0; *p*=1.0). The number of subtypes of ELS experienced by each subject (X^2=7.49; *d.f.*=5.0 *p*=0.18) of both groups and the total score of CTQ (*t*= 1.45; *d.f.*= 42.0; *p*=0.15) was also assessed and compared between groups, but no difference was found. These results are available in Fig. 2.

Insert Fig 2

Concerning scores of each 5 subtypes of ELS, there was no difference between groups for EA (*t* = 1.28; *d.f.* = 42.0; *p* = 0.2), PA (*t* = 0.8; *d.f.* = 42.0; *p* = 0.4), SA (*t* = 1.24; *d.f.* = 42.0; *p* = 0.2), EN (*t* = 1.62; *d.f.* = 42.0; *p* = 0.2), and PN (*t* = 0.82; *d.f.* = 42.0; *p* = 0.9).

Insert Table 3

On table 3, see the assessment of the impact of chronic pain and/or ELS and its subtypes (or their interaction) on depression scores (GRID-HAM-D21). When we analyse if the severity of the depressive symptoms we found a significant impact on the total score of childhood trauma, emotional abuse, physical abuse, emotional neglect and physical neglect; and we found that emotional abuse, sexual abuse and physical neglect have significant impact on the severity of depression, no significant interaction between pain and ELS have been found.

In the figure 3 see the the prevalence of subtypes of ELS, emotional neglect in the group with depression without pain, and in the group with depression with pain (31.8% vs. 68.7%; x^2= 4.46; *d.f.*= 1.0; * *p*=0.03).

Insert Fig 3

DISCUSSION

According to the literature, traumatic events experienced in childhood or adolescence rise individual vulnerability for development of physical and mental disorders, mainly depression (Baes et al., 2012; Carr et al., 2013; Juruena, 2014; Martins et al., 2011, 2014; Juruena et al., 2015; Tofoli et al., 2011).

Most of the subjects that were evaluated in this study experienced ELS. These findings corroborate with data of previous studies that showed high rates of ELS in depressive patients (Arnow et al., 2011; Norman et al., 2012; Seok et al., 2012; Shapero et al., 2013; Wingenfeld et al., 2011), and isolate cases of chronic pain (Davis, Luecken & Zautra, 2005; Finestone, 2000; Goldberg, Pachasoe & Keith, 1999).

Therefore, before our study, there was no other showing that ELS may be more prevalent in patients with chronic pain than without chronic pain. This point denotes the innovative character of this study.

In this study, it was possible to observe that patients with ELS and chronic pain present significant more severe depressive symptoms compared to those depressive patients that do not have ELS and/or pain. The impact of chronic pain in depression has already been demonstrated in the literature (Fayaz et al., 2016; Vos et al., 2012), suggesting that painful symptoms reduce the probability of partial or total remission of depressive symptoms in primary care patients undergoing antidepressants (DeVeagh-Geiss et al., 2010). In our study, the worsening of the depressive symptoms was also evidenced in subjects that presented chronic pain and depression.

Some other studies showed a high frequency of subtypes of ELS in depressive patients, with and without chronic pain (Widom et al., 2007; Brown & Anderson, 1991). Some authors as Teicher (2012) refers that exposition to different subtypes of ELS raises rates of psychiatric disorders development afterwards. Thus, the assessment of subtypes of ELS in our sample may be so relevant for comprehension of influence of ELS and its subtypes in chronic pain and depressive episodes, considering ELS and its subtypes as influencers of those episodes, concerning their severity, response to treatment, and according to previous studies (Douglas & Porter, 2012; Miniati et al., 2010).

It is also important to highlight that stressful events occurred in childhood and adolescence generate structural and functional changes on brain of depressed patients, leading to irreparable impairments to individuals' nervous system that remain over time (Cohen et al., 2001; Heim et al., 2000; Teicher et al., 2002, 2012). Likewise, these changes in the nervous system may be present in all depressive patients with ELS, including in those that compose our sample, given the occurrence of chronic pain is already considered a stressing event that causes irreparable damages to structure and functioning of the nervous system (May, 2008).

Our findings also showed that depressive patients with chronic pain experienced considerably more EN than those without pain. In this perspective, it is important to emphasize that subjects with EN may have some altered or impaired connections among

brain areas responsible for emotion processing, like the amygdala, prefrontal cortex, and hippocampus (White et al., 2012; Maheu et al., 2010; De Bellis, 2005; Teicher 2002). The above mentioned brain areas use to be impaired in depressive (Mayberg et al., 1999; Wang et al., 2015) and pain disorders (Flor, 2000; Martucci & Mackey, 2016), sustaining our findings that EN may be considered a risk factor for comorbidity between depression and pain. According to Sanchs-Ericsson et al. (2009), maladaptive beliefs and impaired cognition are common in subjects with ELS and may potentialize the co-occurrence of mental and many disorders, like depression and chronic pain. Literature shows that the risk of suicide in subjects that were sexually abused is 3 to 6-fold higher than those not exposed to SA (Molnar et al., 2001). Lampe et al. (2003) found that experience of SA or PA may increase the risk for depression and chronic pain throughout life. Other studies that also investigated subtypes of ELS found that EA is related to the emergence of depressive episodes (Carr et al., 2013; Martins et al., 2014; Tunnard et al., 2014).

However, previous studies in literature (As-Sanie et al., 2014; Goldberg, 1994; Sanchs-Ericsson, Kendall-Tackett & Hernandez, 2007) have not documented ELS as a primary factor for comorbidity between depression and chronic pain. Although, this is the first article that shows EN as a risk factor for comorbidity of depression and chronic pain. In this way, these findings confer innovative character to our study. Our data also suggest that in depressive patients, experiencing EN in childhood or adolescence, may increase the risk of developing chronic pain about almost fourfold. In this study, it was not found any relation between other subtypes of ELS, but EN.

Although the importance of our findings, our study presents some limitations. First, the sample size must be considered. The more reduced the sample size, more difficult to find significant results and lower statistical power (Button et al., 2013). Despite the small sample size, our study found significant differences between depressive patients with and without pain. The second limitation is that ELS has a broad definition. In this study, we applied CTQ, which is a gold standard and the most applied instrument to assess the presence or absence of traumatic events in childhood and adolescence, but it only assesses 5 subtypes of ELS: EA, PA, SA, EN, and PN (Bernstein et al., 2003; Carr et al., 2013; Grassi-Oliveira, 2014; Martins et al., 2011). CTQ does not assesses other subtypes of ELS such as the presence of psychiatric disorders in caregivers, divorce or parent's death (Bernstein et al., 2003; Carr et al., 2013; Grassi-Oliveira, 2014; Martins et al., 2011; Schwartz et al., 2005; Bremner et al., 2000; Fink et al., 1995; Parker et al., 1979). The third limitation of this study is that subjects that composed the group depression and chronic pain presented different kinds of pain. Although some studies

showed that different kinds of pain mixed in the same sample do not cause a considerable interference in the main result (Goldenberg, 1994).

CONCLUSION

It is essential that other studies replicate our findings in larger samples for straightening the evidence that pain may worsen depression severity. Our findings indicate that depressive patients with pain experienced significantly more ELS, highlighting EN, than those without pain. Also, those depressive patients with ELS and pain experienced more severe depressive symptoms than those without ELS. Thus, it is possible that those subjects that experienced EN in early-life have higher chances of developing comorbidity between depression and chronic pain.

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Table 1
Sociodemographic characteristcs of participants.

	Depressed Patients (N = 44)			
	With Pain (n = 22)	**Without Pain (n = 22)**	**Statistics**	***p***
***Gender, n* (%)**			□² (d.f.) = 0.61(1.0)	0.43
Female	19(86.4)	17(77.03)		
Male	3(13.6)	5(22.07)		
Age, mean (±SD)	41.91(12.29)	36.55(11.08)	*t* (d.f.) = 1.52(42.0)	0.13
BMI, kg/m², mean (±SD)	28.41(9.13)	27.84(6.29)	*t* (d.f.) =0.24(42.0)	0.81
***Ethinical group, n* (%)**			□² (d.f.)=5.53(3.0)	0.14
White	7(31.8)	14(63.6)		
Yellow	3(13.6)	2(9.1)		
Brown	9(40.9)	3(13.6)		
Black	3(13.6)	3(13.6)		
***Marital Status, n* (%)**			□² (d.f.) = 6.15(3.0)	0.10
Single	3(13.6)	10(45.5)		
Married/Living together	16(72.7)	10(45.5)		
Separeted/Divorced	2(9.1)	2(9.1)		
Widow	1(4.5)	0(0.0)		
***Religion, n* (%)**			□² (d.f.)=1.49(5.0)	0.91
Without religion	5(22.7)	4(18.2)		
Catholic	9(40.9)	10(45.5)		
Testimony of Jehovah	2(9.1)	2(9.1)		
Evangelical	4(18.2)	4(18.2)		
Spirits	1(4.5)	2(9.1)		
Spiritualized	1(4.5)	0(0.0)		
***Education levels, n* (%)**			□² (d.f.)=8.28(6.0)	0.21
Middle School Uncompleted	6(27.3)	2(9.1)		
Middle School Completed	1(4.5)	2(9.1)		
High School Uncompleted	3(13.6)	1(4.5)		
High School Completed	6(27.3)	6(27.3)		
College Uncompleted	2(9.1)	5(22.7)		
College Completed	3(13.6)	1(4.5)		
Postgraduated	1(4.5)	5(22.7)		

Note**:** ***d.f.*:** degree of freedom; *SD:* Standard deviation; □²: Chi-square test; *p*: significance level; *t*: Student *t* test.

Table 2
Clinical and psychiatric characteristics of participants.

	Depressed Patients (N=44)			
	With Pain (n=22)	**Without Pain (n=22)**	**Statistics**	***p***
***Smoking, n* (%)**	4(18.2)	4(18.2)	χ^2 (d.f.) = 0.0(1.0)	1.00
Alcoholism, n (%)	0(0.0)	0(0.0)	-	1.00
Use of illicit substances, n (%)	0(0.0)	0(0.0)	-	1.00
Clinical diseases, n (%)	22(100)	10(45.5)	χ^2 (d.f.) = 16.50(1.0)	≤0.001***
***Diagnostic, n*(%)**			χ^2 (d.f.) = 0.91(1.0)	0.34
Unipolar	16(72.7)	13(59.1)		
Bipolar	6(27.3)	9(40.9)		
***Onset of depression, age,* mean(±*SD*)**	24.82(7.38)	23.27(12.74)	*t* (d.f.) = 0.49(42.0)	0.07
***Number of suicide attempts,* mean(±SD)**	1.68(2.49)	1.23(2.32)	*t* (d.f.) = 0.53(42.0)	0.87
***Previous psychiatric hospitalization, n* (%)**	8(36.4)	4(18.2)	χ^2 (d.f.) = 1.83(1.0)	0.17
Familiar history of mental disorders, n (%)	18(81.8)	19(86.4)	χ^2 (d.f.) = 0.17 (1.0)	0.68
Psychiatric Comorbidities, n (%)	19(86.4)	16(72.7)	χ^2 (d.f.) = 5.28(37.0)	0.02*

Note**:** SD: Standard deviation; χ^2: Chi-square test; *t*: Student t test; *p*: significance level; **p≤0.05; ***p≤0.001.*

Figure 1a. Evaluation of the presence of ELS among the depressed participants of the study (χ^2= 3.77; *d.f.*= 1.0; *: *p*=0.05).

Note: ELS: Early-Life Stress; X^2: Chi-Square test.

Figure 1b. Assessment of intensity of depressive symptoms among subgroups with depression in the presence or absence of pain and ELS.

(F=2.753; *d.f:* 3.0; p=0.055; *posthoc* test [NO PAIN/NO ELS x PAIN/ELS]: -4.650; *p*=0.046)

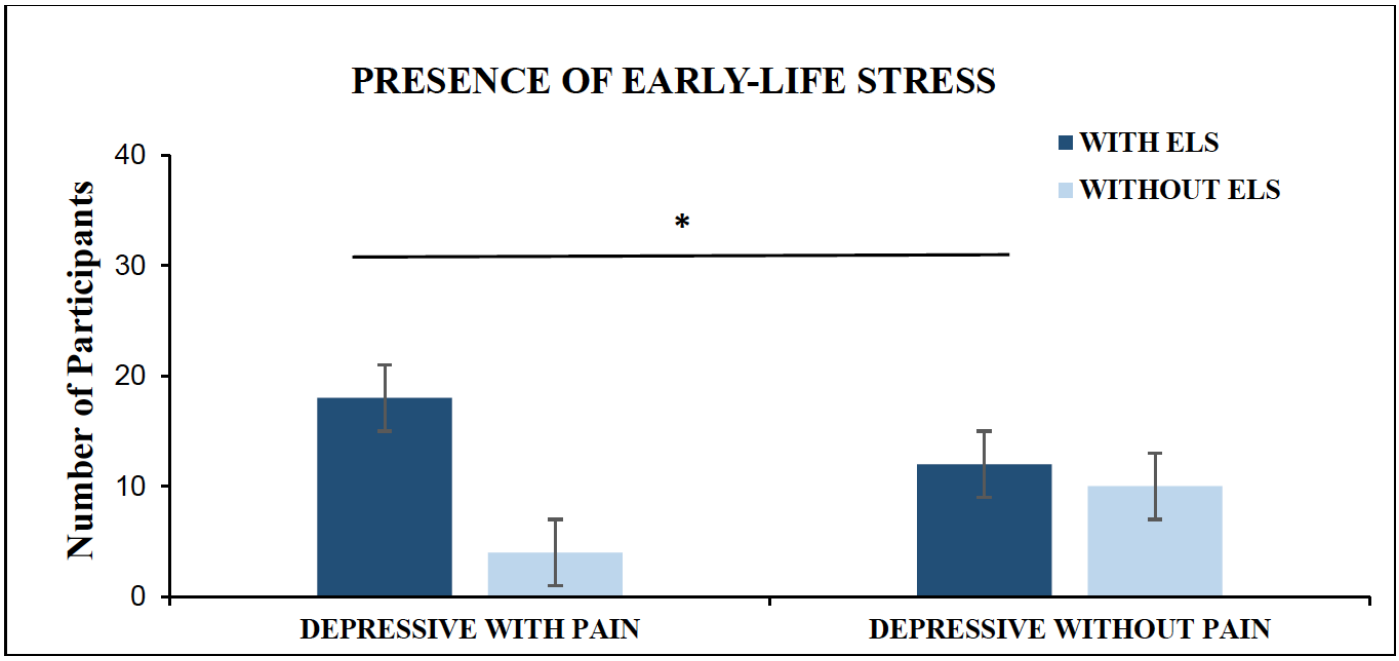
Note: ELS: Early-Life Stress; GRID-HAM-D21: GRID-Hamilton Rating Scale for Depression.

Figure 2. Assessment of the presence of ELS subtypes in the depressed patients of the study. Emotional Abuse: (χ^2=0.09; *d.f.*=2.0; *p*=0.76)*;* Physical Abuse (χ^2=0.58; *d.f.*=2.0; *p*=0.45); Sexual Abuse (χ^2=1.62; *d.f.*=1.0; *p*=0.44); Emotional Neglect (χ^2= 4.46; *d.f.*= 1.0; *p*=0.03) e Physical Neglect (χ^2=0; *d.f.*=1.0; *p*=1.0); *: $p \leq 0.05$.

Note: CTQ: Childhood Trauma Questionnaire; χ^2*:* Chi-Square test.

Figure 3. Prevalence of emotional neglect in the group with depression without pain, and in the group with depression with pain (31.8% vs. 68.7%; $\chi^2 = 4.46$; *d.f.*= 1.0; * $p=0.03$).

Figure



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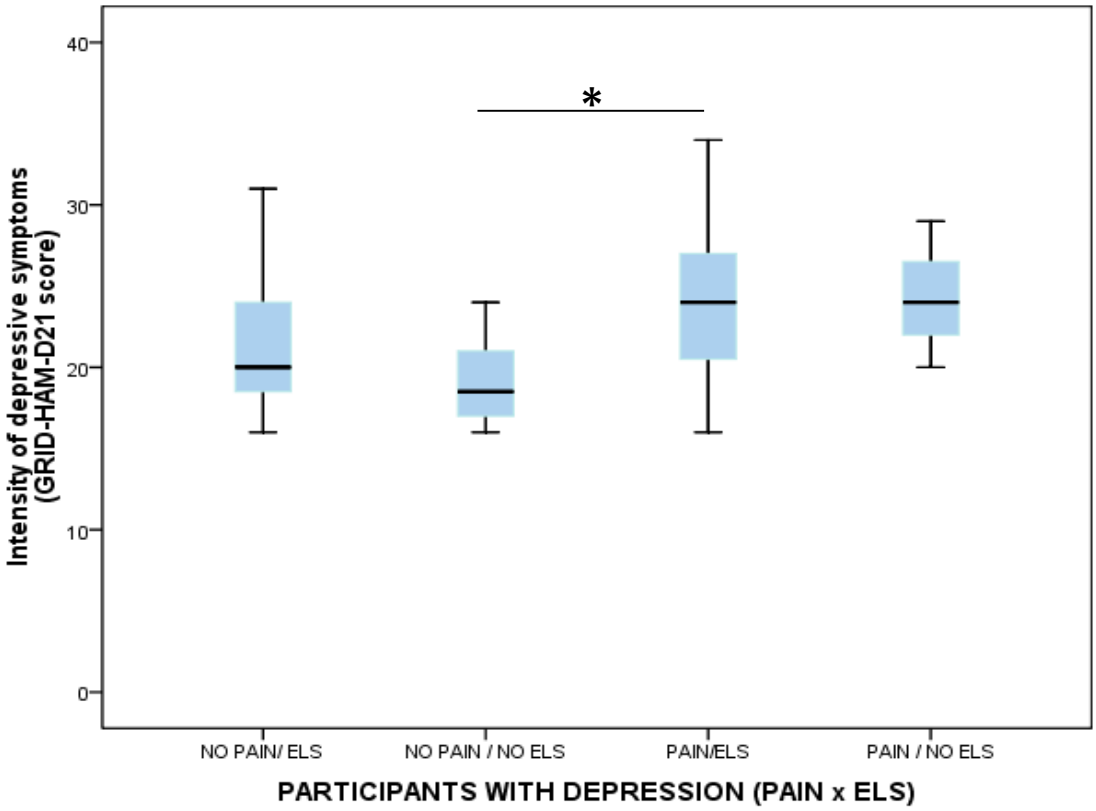

NO PAIN/NO ELS (n=10)	NO PAIN/ELS (n=11)	PAIN/NO ELS (n=3)	PAIN/ELS (n=20)
19.00 ± 2.49	21.64 ± 4.63	24.33 ± 4.51	23.65 ± 4.98

Figure 1b. Assessment of intensity of depressive symptoms among subgroups with depression in the presence or absence of pain and ELS.
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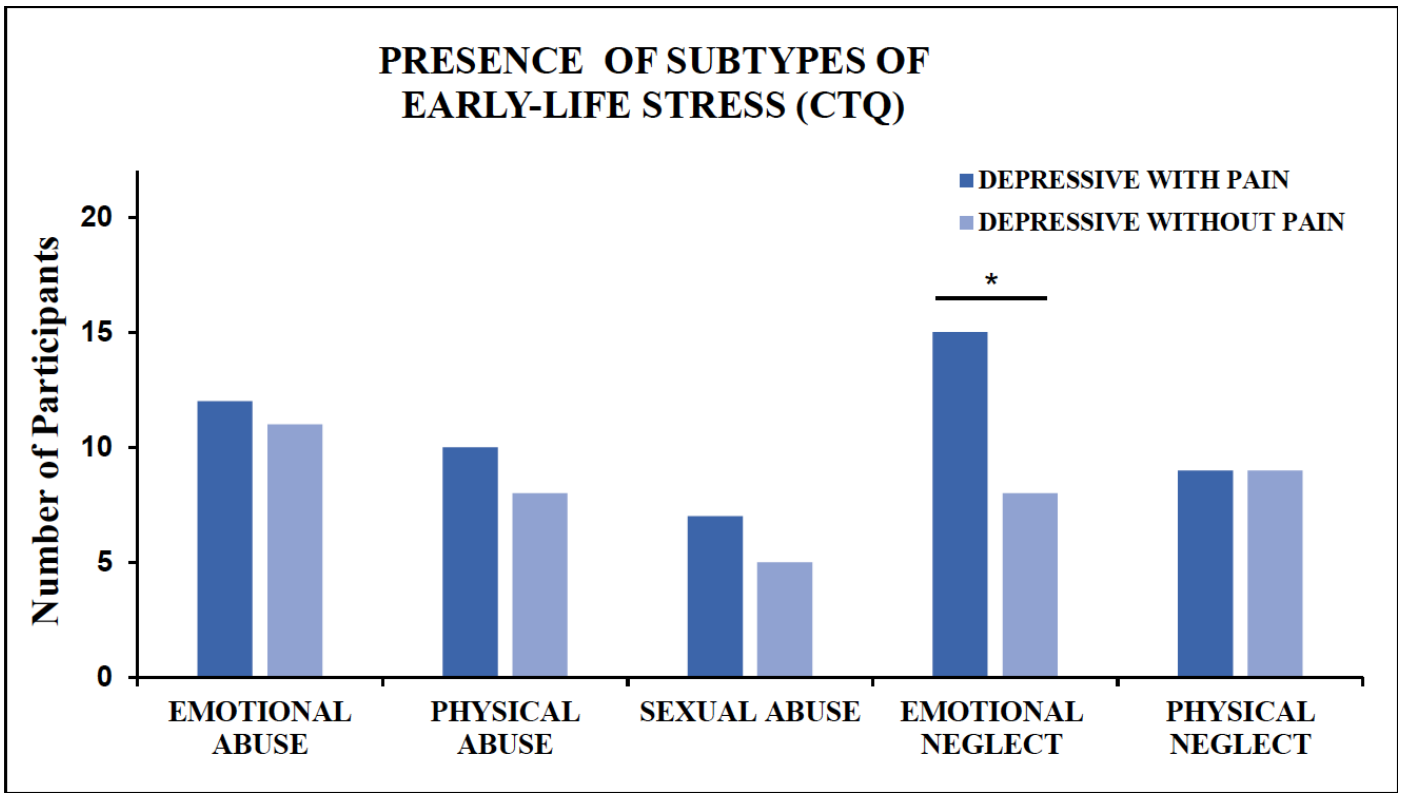

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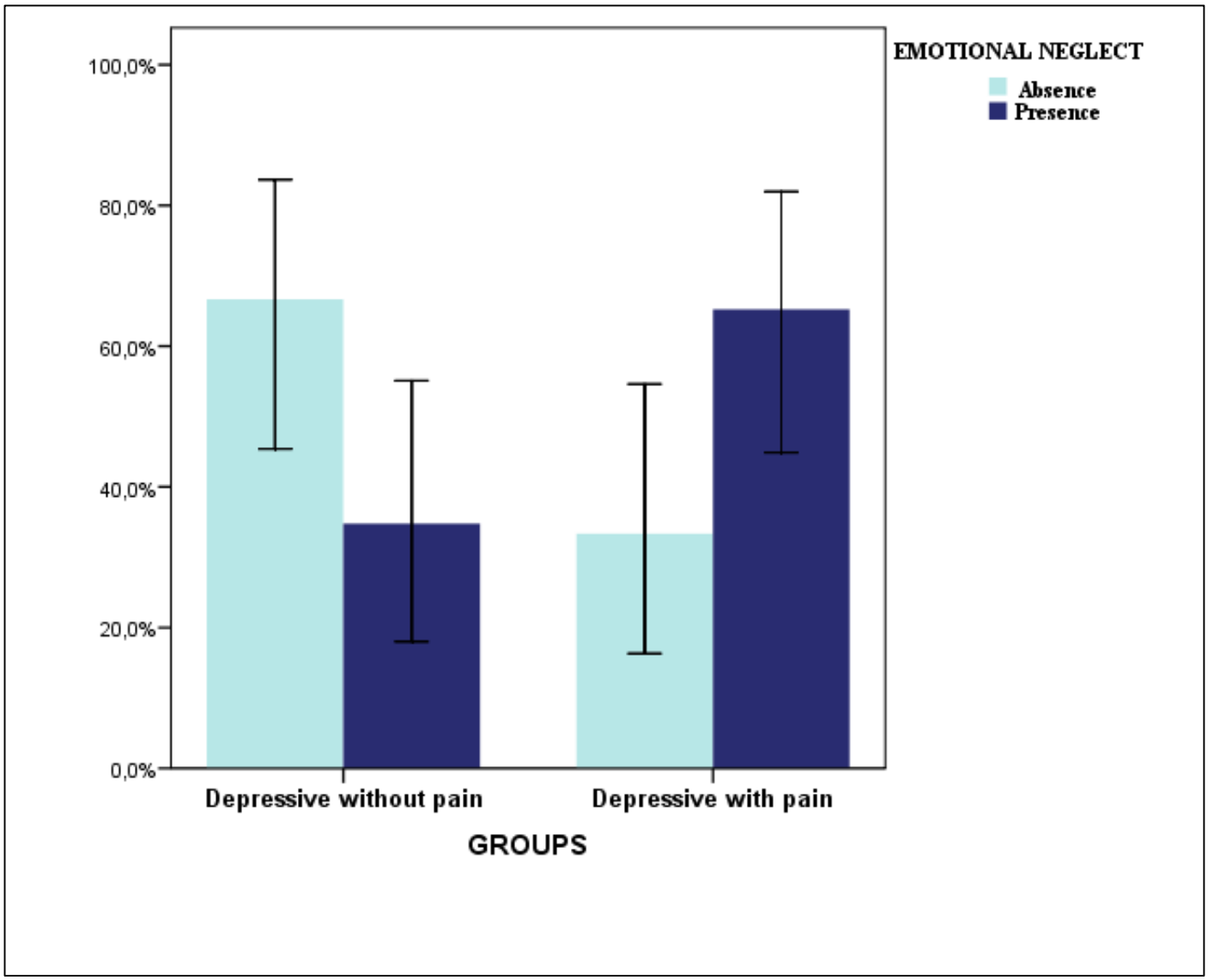

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Spirits	1(4.5)	2(9.1)		
Spiritualized	1(4.5)	0(0.0)		
***Education levels, n* (%)**			χ^2 (d.f.)=8.28(6.0)	0.21
Middle School Uncompleted	6(27.3)	2(9.1)		
Middle School Completed	1(4.5)	2(9.1)		
High School Uncompleted	3(13.6)	1(4.5)		
High School Completed	6(27.3)	6(27.3)		
College Uncompleted	2(9.1)	5(22.7)		
College Completed	3(13.6)	1(4.5)		
Postgraduated	1(4.5)	5(22.7)		

Note**:** *d.f.:* degree of freedom; *SD:* Standard deviation; χ^2: Chi-square test; *p*: significance level; *t*: Student t test.

Table 2 Clinical and psychiatric characteristics of participants.

Depressed Patients (N=44)				
	With Pain (n=22)	**Without Pain (n=22)**	**Statistics**	***p***
***Smoking, n* (%)**	4(18.2)	4(18.2)	χ^2 (d.f.) = 0.0(1.0)	1.00
Alcoholism, n (%)	0(0.0)	0(0.0)	-	1.00
Use of illicit substances, n (%)	0(0.0)	0(0.0)	-	1.00
Clinical diseases, n (%)	22(100)	10(45.5)	χ^2 (d.f.) = 16.50(1.0)	≤0.001***
***Diagnostic, n*(%)**			χ^2 (d.f.) = 0.91(1.0)	0.34
Unipolar *Bipolar*	16(72.7) 6(27.3)	13(59.1) 9(40.9)		
***Onset of depression, age,* mean(±*SD*)**	24.82(7.38)	23.27(12.74)	*t* (d.f.) = 0.49(42.0)	0.07
***Number of suicide attempts,* mean(±SD)**	1.68(2.49)	1.23(2.32)	*t* (d.f.) = 0.53(42.0)	0.87
***Previous psychiatric hospitalization, n* (%)**	8(36.4)	4(18.2)	χ^2 (d.f.) = 1.83(1.0)	0.17
Familiar history of mental disorders, n (%)	18(81.8)	19(86.4)	χ^2 (d.f.) = 0.17 (1.0)	0.68
Psychiatric Comorbidities, n (%)	19(86.4)	16(72.7)	χ^2 (d.f.) = 5.28(37.0)	0.02*

Note**:** SD: Standard deviation; χ^2: Chi-square test; *t*: Student t test; *p*: significance level; **p≤0.05; ***p≤0.001.*

Table 3. Assessment of impact of chronic pain and/or ELS and its subtypes (or their interaction) on GRID-HAM-D21 scores

	PAIN	ELS (or its subtypes)	INTERATION PAIN*ELS (or its subtypes)
ELS	**F=6.280; p=0.016**	F=0.739; p=0.395	F=0.387; p=0.538
EA	**F=8.519; p=0.006**	**F=5.048; p=0.030**	F=0.088; p=0.769
PA	**F=6.382; p=0.016**	F=1.801; p=0.179	F=0.912; p=0.345
SA	F=3.936; p=0.054	**F=3.464; P=0.041**	F=1.024; p=0.318
EN	**F=7.189; p=0.011**	F=0.537; p=0.468	F=3.140; p=0.084
PN	**F=7.736; p=0.008**	**F=2.394; p=0.130**	F=0.554; p=0.461

Note: EA: emocional abuse; ELS: Early-life stress; EN: emocional neglect; GRID-Hamilton Rating Scale for Depression; PA: physical abuse; PN: physical neglect; SA: sexual abuse.